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HYPNOTICS AND ANTICONVULSANTS. I. TERTIARY ACETYLENIC CARBINOLS

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The current revival[1] of interest in the hypnotic (1, 2) and anticonvulsant (2, 3) properties of tertiary acetylenic carbinols has prompted us to prepare a series of such compounds for pharmacological evaluation. The new compounds prepared are listed in Table I with their respective physical properties, analyses, and pharmacological activities. Several known compounds are included for comparison, or because they were prepared by a different method or were incompletely characterized in the earlier literature.

Most of the carbinols were prepared by the reaction of an alkali metal acetylide with a ketone in liquid ammonia. Since lithium acetylide has been found to give higher yields and less polymerization than the more strongly basic sodium acetylide in the addition to vinyl ketones, lithium acetylides were used in the preparation of most of the compounds reported here. The general procedures used are denoted by letter in Table I and described in the Experimental section; specific variations in experimental conditions not described in the Experimental section are given in footnotes to the Table.

Method A consists simply of the addition of the appropriate ketone (in ether solution) to a solution of lithium acetylide, prepared from lithium metal, in liquid ammonia. Method A′ is similar except that the lithium salt of an alkyne is used instead of lithium acetylide.

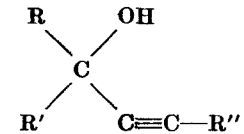
Method B is a convenient new procedure for the preparation of acetylenic carbinols derived from vinyl ketones, since it obviates the necessity for preparing the vinyl ketone as such. Although alkyl β-chloroethyl ketones are readily obtained by the addition of acid chlorides to ethylene (4–6), they can usually be dehydrochlorinated to the vinyl ketones only in low yield, especially on a larger scale (4, 5). Treatment of the alkyl β-chloroethyl ketones directly with two equivalents of lithium acetylide in liquid ammonia (Method B), however, led to the desired alkyl vinyl ethynyl carbinols II–V in good yields. The β-chloroketone is dehydrohalogenated by one equivalent of lithium acetylide, and the vinyl ketone formed is protected from undesirable reactions by the low temperature and by rapid reaction with the remaining lithium acetylide. One compound (XIII) was prepared by a similar method (B′) from ethyl β-chloroethyl ketone and the lithium salt of propyne.

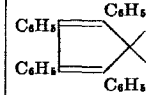
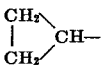
The alkyl β-chloroethyl ketones required were prepared from the appropriate acid chlorides and ethylene according to the known procedures (4–7). These intermediates were usually contaminated with some of the corresponding vinyl

[1] The pharmacology of tertiary acetylenic carbinols appears to have been first investigated in 1930 by H. Bock (Inaugural-Dissertation, *Zur Pharmakologie ungesättiger Alkohole*, Pharmakol. Inst. der Univ. Breslau, 1930). We are indebted to Mr. Harold Oatfield for calling this early work to our attention.

TABLE I

TERTIARY ACETYLENIC CARBINOLS



No.	R	R'	R''	METHOD	YIELD, %	B.P. °C.	B.P. MM.	n_D^{25}	d_4^{20}	FORMULA	ANALYSES Calc'd C	Calc'd H	Found C	Found H	ACTIVITIES[a] Hypnotic mg./kg.	Anticonvulsant mg./kg.
I[b,c]	CH_3—	CH_2=CH—	—H	A		24.5–25	12		0.8665						376	89
II	C_2H_5—	CH_2=CH—	—H	B	73	68.5–69	48	1.4493	.866	$C_7H_{10}O$	76.32	9.15	76.19	9.04	180	53
III	n-C_3H_7—	CH_2=CH—	—H	B	37[d]	98–99	102		.873	$C_8H_{12}O$	77.37	9.74	76.76	9.66	400	400
IV	iso-C_3H_7—	CH_2=CH—	—H	B	59.3	65–66	29	1.4520	.892	$C_8H_{12}O$	77.37	9.74	77.53	10.03	150	38
V	n-C_4H_9—	CH_2=CH—	—H	B	60.8	66–68	9	1.4532	.877	$C_9H_{14}O$	78.21	10.21	78.26	10.25	310	70
VI	CH_3—	CH_2=C(CH_3)—	—H	A	63.2	83–84	100	1.4538	.875	$C_7H_{10}O$	76.32	9.15	76.31	9.33	265	50
VII[b,c]	CH_3—	$(CH_3)_2$C=CH—	—H	A	31	66–66.5	16	1.4618	.894						262	79
VIII			—H	A		[e]				$C_{31}H_{22}O$	90.70	5.40	90.49	5.61	>400	>400
IX[f]	CH_3—		—H	A, D	41.8	54–55	19	1.4553	.917	$C_7H_{10}O$	76.32	9.15	75.99	9.19	180	66
X[g]	CH_3—	CH_3—CO—	—H	A	28.9	82–87	52	1.4661	.846	$C_6H_8O_2$	64.27	7.19	64.18	7.45	>400	250
XI	CH_3—	$C_2H_5O_2C$—$(CH_2)_2$—	—H	A	30.6	72–73	0.5	1.4491	1.032	$C_9H_{14}O_2$	63.51	8.29	63.66	8.13	>400	>400
XII	CH_3—	CH_2=CH—	—CH_3	A′	32.9	96–97	101		.892	$C_7H_{10}O$	76.32	9.15	75.7	9.24	500	250
XIII	C_2H_5—	CH_2=CH—	—CH_3	B′	11.5	68–69	15	1.4670	.905	$C_8H_{12}O$	77.37	9.74	77.16	9.88	350	300
XIV	CH_3—	CH_2=CH—	n-C_3H_7	C	49.5	81.5–82	18	1.4552	.878	$C_9H_{14}O$	78.21	10.21	78.05	10.19	400	>400
XV	CH_3—	CH_2=CH—	n-C_4H_9	C	44.3	92–93	15	1.4555	.870	$C_{10}H_{16}O$	78.90	10.60	78.83	10.36	750	>500
XVI	CH_3—	CH_2=CH—	n-C_5H_{11}—	C	40.8	92–93	3	1.4570	.846	$C_{12}H_{20}O$	79.94	11.18	79.86	11.16	500	>500
XVII	CH_3—	CH_2=C(CH_3)—	—CH_3	A′	51.1	68.7–69.5	15	1.4665	.857	$C_6H_{12}O$	77.37	9.75	77.55	9.77	350	250
XVIII	CH_3—	CH_2=CH—	—$CH_2N(C_2H_5)_2$	A′	24.2	130–133	22		.914	$C_{11}H_{13}NO$	72.87	10.56	73.15	10.38	>500[h]	>500
XIX	C_2H_5—	C_2H_5—	—CH_2OH	C′	21.8	81–82.5	0.07	1.4794[i]		$C_6H_{14}O_2$	67.57	9.92	67.46	10.06	400	150
XX[j]	CH_3—	C_2H_5—	—COOH	[k]	13.0	[m]				$C_7H_{10}O_3$	59.14	7.09	59.28	7.05	400	>400
XXI	CH_3—	C_2H_5—	—$COO^{\ominus}$ $H_3N^{\oplus}$—$CH_2C_6H_5$	[k]	21.0	[n]				$C_{14}H_{19}NO_2$	67.45	7.68	67.48	7.69	500	>100
XXII	CH_3	C_2H_5—	—$CONH_2$	[k]		[o]				$C_7H_{11}NO_2$	59.55	7.86	59.29	7.70	400	>300

[a] Figures preceded by a > sign indicate that no activity was observed at those dosage levels. [b] Physical constants given for known compounds are those determined in this laboratory. [c] Hennion and Lieb, *J. Am. Chem. Soc.*, **66**, 1289 (1944); Cymerman, Heilbron, and Jones, *J. Chem. Soc.*, 90 (1945). [d] The lower yield in this case was due to the use of only one equivalent of lithium acetylide with the β-chloroketone. [e] The carbinol was accompanied by considerable recovered tetraphenylcyclopentadienone, from which it could be separated only by chromatography on alumina. [f] Ref. (10). [g] Kleinfeller, *Ber.*, **72**, 249 (1939); Kubota and Takeshima, *J. Sci. Research Inst. (Tokyo)*, **44**, 186 (1950) [*Chem. Abstr.*, **45**, 5106 (1951)]. [h] Tested pharmacologically as the citrate, m.p. 137.4–137.9°. [i] n_D^{23}. [j] Ref. (8). [k] See Experimental. [l] M.p. 193–194°. [m] M.p. 57.6–58.4°. [n] M.p. 145.8–146.2°. [o] M.p. 116–117°.

ketones, and no effort was made to purify them sufficiently for complete characterization.

Most of the carbinols in which R″ is alkyl were prepared from the ketone and the alkyne with lithium amide in liquid ammonia (Method C) in order to prevent wasteful reduction of the valuable alkynes by lithium metal. In one case (XIX), sodium amide was used instead of lithium amide (Method C′).

In the preparation of the acid XX (8), 3-methyl-1-pentyn-3-ol was converted to its sodium salt with sodium amide in liquid ammonia, the ammonia was replaced by toluene, and the salt was carbonated (9), as described in the Experimental section.

Finally, one of the carbinols (IX) was obtained in very low yield by Method A, and the major product was the symmetrical acetylenic glycol. The preparation of this carbinol by the older Favorskii method has been reported (10), and a modification (11) of this method, employing acetylene and powdered potassium hydroxide suspended in dimethyl formal, was found to give IX in somewhat better yield. Considerable glycol was again formed, but it was found that the glycol, in accord with its ease of formation, readily underwent the reverse reaction, to give a considerable further amount of carbinol, when it was heated with anhydrous potassium carbonate at 125° under reduced pressure. The yield reported for IX in the Table is based on total carbinol, including that obtained from the glycol.

The liquid carbinols were usually obtained analytically pure after two simple distillations; in a few cases fractionation was necessary. Slow fractional distillation of compound XI, however, gave a less pure product due to the formation of a small amount of lactone, as indicated by the appearance of a new carbonyl band (weak) at 5.64 μ in the infrared spectrum. All of the carbinols showed a sharp hydroxyl absorption band at or near 2.8 μ, and the ethynyl carbinols all displayed a sharp, moderately strong absorption band at 3.05–3.1 μ, characteristic of mono-substituted acetylenes. The latter band was missing from the spectra of the alkynyl carbinols (R″ = alkyl), and these compounds usually showed instead a weak band at 4.5 μ, characteristic of fully substituted acetylenes.

The carbinols were screened for hypnotic and anticonvulsant (antimetrazole) activities by methods previously described (2). Four to ten mice were used at each dosage level, but since a complete evaluation was made of only a few of the compounds, most of the results reported in the last two columns of Table I are necessarily approximate. Hypnotic activity is defined as the dose in mg. per kg. of body weight which causes sleep in 50% of the mice used. Anticonvulsant effect is similarly indicated by the amount of the compound which protects 50% of the mice from metrazole-induced seizure.

EXPERIMENTAL

Method A. Addition of lithium acetylide to a ketone. To about 600 ml. of liquid ammonia in a 1 l., 3-neck flask, equipped with a stirrer, Dry-Ice condenser, and gas inlet tube, is added 7.6 g. (1.1 moles) of lithium metal in small pieces. Acetone-free acetylene is passed into the stirred solution at about 1 l. per minute until the blue color is discharged and the

gray solid disappears to give a clear solution. The gas inlet tube is then replaced by a dropping-funnel, and the ketone is added in an equal volume of ether during about 15 minutes. The reaction mixture is stirred under reflux for about 2 hours, diluted with approximately 300 ml. of ether, and the ammonia is allowed to evaporate overnight with stirring. The residual suspension is poured into a stirred mixture of ice and acetic acid (66 g., 1.1 moles), and the aqueous layer is separated and re-extracted with ether. The combined ether extracts are washed, dried, and concentrated; and the carbinol is distilled twice at reduced pressure.

Method A'. The reaction is carried out as described under Method A except that an alkyne[2] is used instead of acetylene.

Method B. Reaction of an alkyl β-chloroethyl ketone with two equivalents of lithium acetylide. The reaction conditions are essentially those described under Method A except that two equivalents of lithium (15.4 g.) are used and the volume of ammonia is doubled (*ca.* 1200 ml.). On addition of the alkyl β-chloroethyl ketone, a rapid precipitation of lithium chloride is observed, followed by normal addition of lithium acetylide to the vinyl ketone. The reaction is worked up and the product isolated as described under Method A.

Method B'. Compound XIII was prepared from 1-chloropentanone-3 essentially according to Method B, with the substitution of propyne for acetylene.

Method C. Addition of an alkyne to a ketone with lithium amide in liquid ammonia. To a stirred suspension of 12.1 g. (0.525 mole) of commercial lithium amide in 400 ml. of liquid ammonia is added 0.60 mole of the alkyne in an equal volume of ether during one-half hour. The mixture is stirred vigorously for a few minutes and then treated during 15 minutes with a solution of 0.50 mole of the ketone in 50 ml. of ether. Stirring is continued under reflux for 2–3 hours and the ammonia is allowed to evaporate overnight with stirring. The reaction is then worked up and the product isolated as described under Method A.

Method C' is similar to Method C except that two equivalents of sodium acetylide, prepared *in situ* from sodium (12), are used with propargyl alcohol[3] to give compound XIX.

Method D. Methyl cyclopropyl ketone (58.2 g., 0.69 mole) is treated with acetylene in the presence of powdered potassium hydroxide (116 g., 2.07 moles) suspended in dimethyl formal (187 ml.) according to the modified Favorskii conditions of Zeltner and Genas (11). The reaction mixture is decomposed with ice and acetic acid (125 g., 2.08 moles), and the aqueous layer is separated and extracted with ether. The combined organic extracts are washed, dried, and evaporated. Distillation of the residue affords 28.7 g. of low-boiling material (b.p. 26–56° at 15 mm.) and 27.7 g. of the symmetrical glycol (b.p. 95–98° at 0.4 mm.). The glycol fraction is stirred with 4.0 g. of anhydrous potassium carbonate and is heated slowly to about 125° under reduced pressure. The crude carbinol that distills (26 g.) is combined with the 28.7 g. of low-boiling material from the first distillation and fractionated through a 2 ft. packed column to remove a forerun (9.9 g.), b.p. 24–50° at 16 mm., which consists largely of recovered methyl cyclopropyl ketone. The column is washed down with ether and the residue is subjected twice to simple distillation to give 31.8 g. (41.8% yield) of pure methyl cyclopropyl ethynyl carbinol, b.p. 54–55° at 19 mm.

Preparation of 3-hydroxy-3-methylpent-2-ynoic acid. To a solution of sodium amide prepared from 37.5 g. (1.63 moles) of sodium (12) in liquid ammonia (1.5 l.) was added 73.6 g. (0.75 mole) of 3-methyl-1-pentyn-3-ol during 15 minutes. The mixture was stirred under reflux for 30 minutes, 750 ml. of dry toluene was added (9), and the ammonia was allowed to evaporate with stirring overnight. Most of the remaining ammonia was removed by passing a stream of dry nitrogen through the stirred mixture for 4 hours. The sodium salt of the carbinol was then carbonated by the addition of 300 g. of Dry-Ice in small pieces. Water (700 ml.) was added, the organic layer was separated, and the aqueous layer was extracted three times with ether. The organic extracts were washed with 300 ml. of 5% sodium carbonate, which was then combined with the original aqueous layer, filtered, and acidified by

[2] All of the alkynes used in this work, as well as 1-diethylamino-2-propyne, were purchased from Farchan Research Laboratories.

[3] We are indebted to General Aniline and Film Corp. for a sample of propargyl alcohol.

addition to a slurry of ice and sulfuric acid (105 g.) in the presence of ether. The aqueous layer was saturated with sodium chloride and extracted thoroughly with ether. The combined ether extracts were washed with a saturated sodium chloride solution and dried overnight with sodium sulfate. The dried solution was concentrated to 700 ml., cooled to 10–15°, stirred, and treated gradually with a solution of 87 g. (0.81 mole) of freshly distilled benzylamine in 100 ml. of ether. The salt separated as a mass of white needles, which were filtered and washed with ether; yield 39.2 g. (21.0%); m.p. 145.4–146.2°. The salt was recrystallized for analysis from methanol-ether; white needles, m.p. 145.8–146.2°.

A portion of the benzylamine salt (12.5 g.) was treated with 10% sulfuric acid (25 ml.) and the acid was isolated by ether extraction. Since the acid did not crystallize readily and distilled with some decomposition, it was purified by short-path distillation at 100° (0.1 mm.). After a second such distillation, the pure acid (4.4 g., 13.0% yield from 3-methyl-1-pentyn-3-ol) was obtained as colorless crystals, m.p. 57.6–58.4°.

The *amide* was prepared from crude acid from an earlier experiment by conversion of the acid to the methyl ester with diazomethane and treatment of the distilled ester (b.p. 60–85° at 0.2 mm., with some decomposition) with methanolic ammonia. Concentration of the mixture gave the solid amide, which was recrystallized twice from methanol-benzene to give colorless needles, m.p. 116–117°.

SUMMARY

A number of tertiary acetylenic carbinols have been prepared for evaluation as hypnotics and anticonvulsants. Most of these compounds were prepared by variations of the conventional method, involving the addition of an alkali metal acetylide to a ketone in liquid ammonia. A useful modification for the preparation of carbinols derived from vinyl ketones consists of the reaction of an alkyl β-chloroethyl ketone with two equivalents of lithium acetylide.

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